SYNOPSIS:

"Synthesis and Pharmacological Activity studies of New Pyrazoline, Benzodiazepines and Benzothiazepines Derivatives "

Submitted to

Swami Ramanand Teerth Marathwada University Nanded

For The Registration of Degree of Doctor of Philosophy (Ph. D)

Under The Faculty of Science and Technology the Subject of Organic Chemistry.

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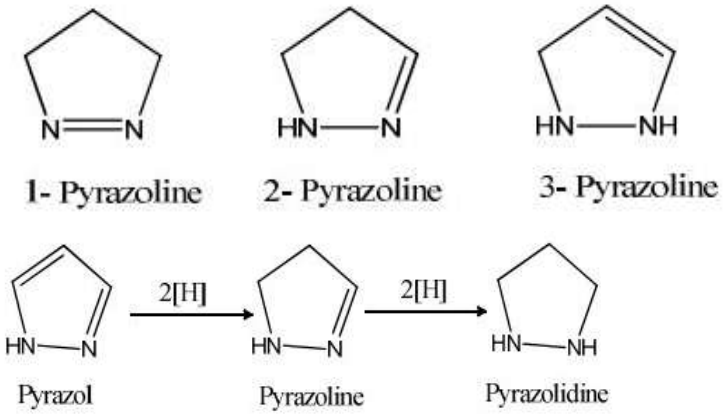
1. Introduction:

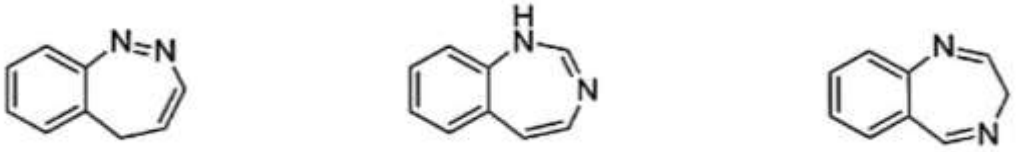
Pyrazoline, also known as dihydropyrazole, is a five-membered heterocyclic compound with the chemical formula $C_3H_6N_2$. It features two adjacent nitrogen atoms and a single endocyclic double bond. Pyrazoline exist in three isomeric forms, which can interconvert through heating and acid catalysis (Figure 1).



(Fig.1)

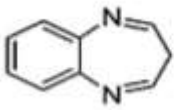
The 2-pyrazoline derivatives are notably stable and exhibit a wide range of biological activities, making them highly significant in pharmaceutical research and drug development. They are considered a valuable medicinal scaffold for the synthesis of new compounds with properties such as antimicrobial, antioxidant, antidiabetic, anticonvulsant, antidepressant, anti-inflammatory, anticancer effects, and monoamine oxidase inhibition[1]. Pyrazole, a term introduced by Ludwig Knorr in 1883, refers to a class of simple aromatic organic compounds that belong to the heterocyclic series. These compounds are characterized by a five-membered ring structure with three carbon atoms and two nitrogen atoms adjacent to each other. Although pyrazoles are classified as alkaloids due to their pharmacological effects on humans, they are relatively uncommon in nature. The first natural pyrazole, 1-pyrazolyl-alanine, was discovered in 1959 in watermelon seeds[2].

Benzodiazepines are nitrogen heterocycles having a six-membered benzene ring system fused to a seven-membered fused ring system with two nitrogen atoms [3]. Benzodiazepines are classified into six types of classes, these are depends upon the position of the heteroatom Nitrogen in the ring. (Figure 2)



1,2-benzodiazepine 1,3-benzodiazepine 1,4-benzodiazepine

1 2 3



1,5-benzodiazepine

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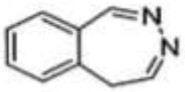

2,3-benzodiazepine

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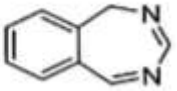
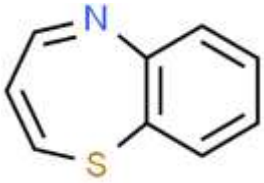


2,4-benzodiazepine

6

(Fig-2)

Benzothiazepines are a bicyclic heteroaromatic compound featuring a seven-membered ring containing nitrogen and sulfur, which is attached to a benzene structure [4]. (Figure.3).



Benzothiazepines

(Fig. 3)

2. The importance of the proposed research:

1. **Pyrazoline** derivatives exhibit a broad range of biological activities and are effectively used as anti-inflammatory, antimalarial, antidepressant, and antimicrobial agents[5]. Due to their is high stability and diverse biological activities of 2-pyrazoline derivatives, they hold significant importance in pharmaceutical chemistry research and drug discovery. They are considered a potent medicinal scaffold for synthesizing new derivatives with activities such as antimicrobial, antioxidant, antidiabetic, anticonvulsant, antidepressant, anti-inflammatory, anticancer, and monoamine oxidase inhibition[6].
2. **Benzodiazepines** are a crucial class of compounds with diverse therapeutic and biological activities. They are widely used for their antianxiety, sedative, antidepressive, anticonvulsant, neuroleptic, and hypnotic properties. Additionally, benzodiazepine derivatives have shown efficacy as anti-inflammatory, antiviral, anti-HIV, antimicrobial, and antitumor agents. The benzodiazepine nucleus is also integral in various pharmacological applications, including antihypertensive, antiasthmatic, analgesic, cardiovascular modulation, vasodilation, platelet aggregation inhibition, antiulcer, antidementia, antibacterial, antifungal, and insecticidal activities. Key compounds within this class are used to treat conditions such as HIV infection, epilepsy, psychosis, angina pectoris, hypertension, and arrhythmias[7].
3. **Benzothiazepine** is a key heterocyclic structure with significant relevance in medicinal chemistry, as it is found in various bioactive compounds. It functions as a crucial "biolinker" in the synthesis of bioactive molecules and serves as an essential framework

for developing new compounds. Benzothiazepine derivatives exhibit a wide range of pharmacological activities, including calcium channel blocking, central nervous system effects, anti-HIV properties, ACE inhibition, as well as antimicrobial, antifungal, and anticancer activities [8].

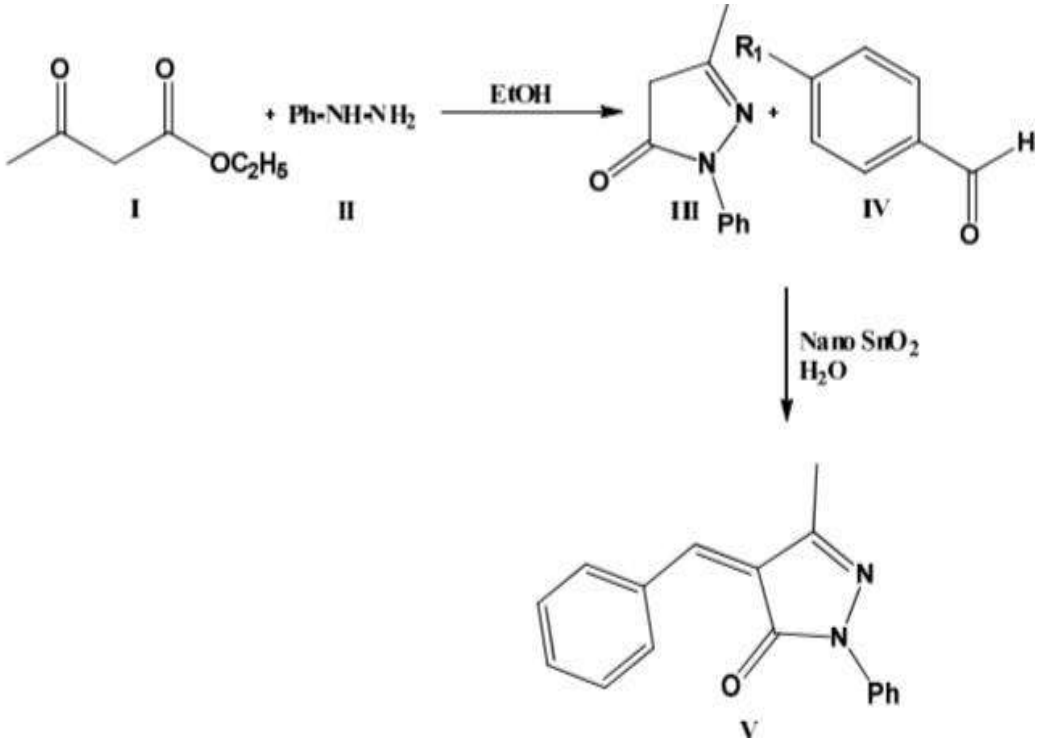
3. Objectives of the research:

1. Review of Previous Studies: Review the scientific literature related to Pyrazoline, Benzodiazepines and Benzothiazepines compounds.
2. Development and Application of New Synthesis Methods: Develop and apply new methods for synthesizing Pyrazoline, Benzodiazepines and Benzothiazepines compounds using different approaches.
3. Spectroscopic Analysis: Perform spectroscopic analysis of the resulting compounds using techniques such as IR spectroscopy and nuclear magnetic resonance (NMR) to determine their chemical structures.
4. Study of Pharmacological Activity: Investigate the pharmacological activity of the prepared compounds.

4. Literature review:

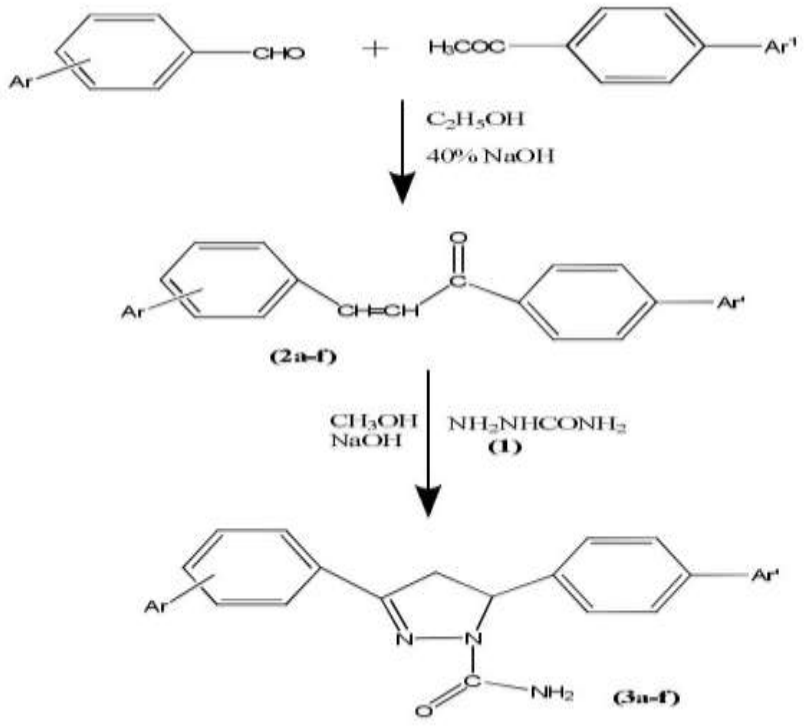
1. Patki *et al* [9]. investigated the synthesis of pyrazole derivatives using ethyl acetate, phenyl hydrazine, and substituted benzaldehyde as starting materials. Their study demonstrated that this method produced pyrazole derivatives with excellent yields. Notably, they observed that the presence of electron-withdrawing groups on aromatic aldehydes positively affect the yield of the pyrazole derivatives, enhancing the overall efficiency of the synthesis process.

   Reactions Scheme:



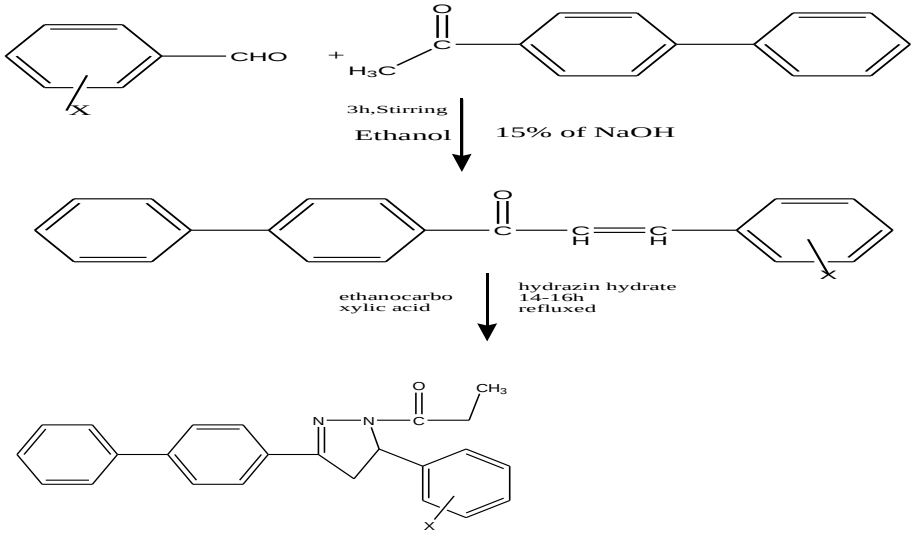
Scheme(1)

2. Revanasiddappa, *et al* [10]. The study focused on synthesizing new pyrazoline derivatives and evaluating their antidepressant activity. Pyrazolines, derived from pyrazole, have various biological activities, including antidepressant effects. The researchers prepared these pyrazoline derivatives using chalcones and semicarbazide. They tested the antidepressant activity of these compounds using the Tail Suspension Test (TST) and the Forced Swimming Test (FST). Among the new compounds, one (3a) showed moderate antidepressant activity compared to the standard drug Imipramine. The compounds were characterized using mass spectrometry (MS), proton nuclear magnetic resonance (H-NMR), and infrared (IR) spectroscopy.



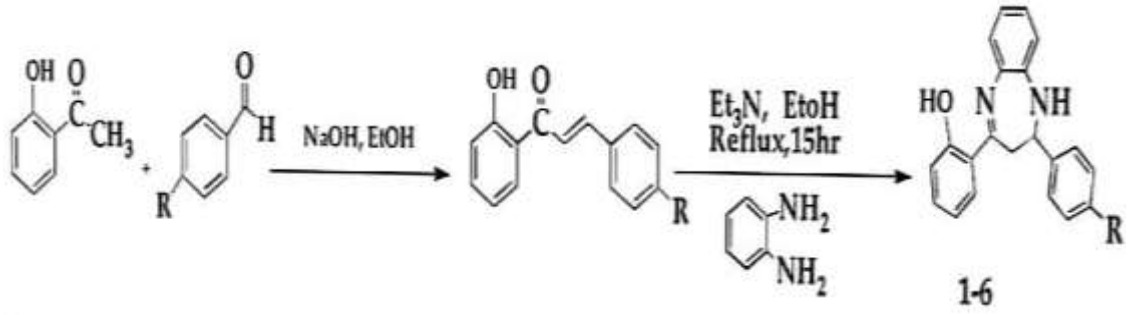
Scheme(2)

3. Chinnamanyakar,*et al* [11] the study focused on the synthesis of new pyrazoline compounds through a multicomponent reaction involving xenyl chalcone and hydrazine hydrate. These compounds were characterized using spectral methods and evaluated for their potential as drug candidates. In-silico ADME (absorption, distribution, metabolism, and excretion) studies suggested they could be orally active. Docking studies with specific proteins indicated promising binding affinities, particularly for one compound selected for further biological evaluation. The antimicrobial activity of the synthesized compounds was also assessed, revealed some with significant effectiveness.



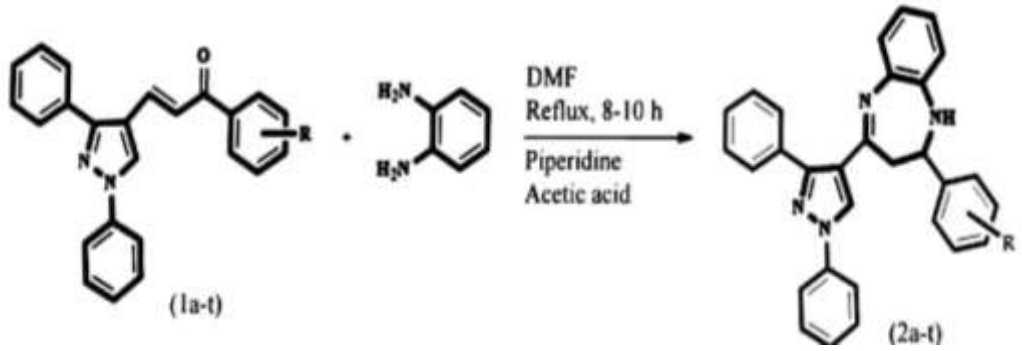
Scheme(3)

4. Haq, Faizan Ul, *et al* [12]. have explored new antidepressant agents by synthesizing and testing various benzodiazepine analogues in mice. After preparing these compounds and confirming their structures, the researchers assessed their antidepressant effects using forced swim and tail suspension tests. Significant reductions in immobility time indicated promising antidepressant activity for certain compounds. Additionally, these compounds enhanced GABA levels in the brain, suggesting a potential mechanism for their antidepressant effect.



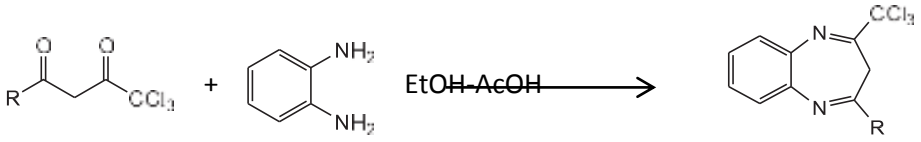
Scheme(4)

5. Desai, N. C., Joshi, S. B., & Khedkar, V. M [13] . have presented a one-pot synthesis of pyrazole derivatives containing benzodiazepine moieties and evaluated their antimicrobial activities. The synthesized compounds were characterized using various spectral techniques. The antimicrobial testing revealed that some derivatives exhibited strong antibacterial and antifungal activities. Molecular docking studies provided insights into the binding interactions of these compounds with the microbial target DNA gyrase, helping to understand their potential as antimicrobial agents.



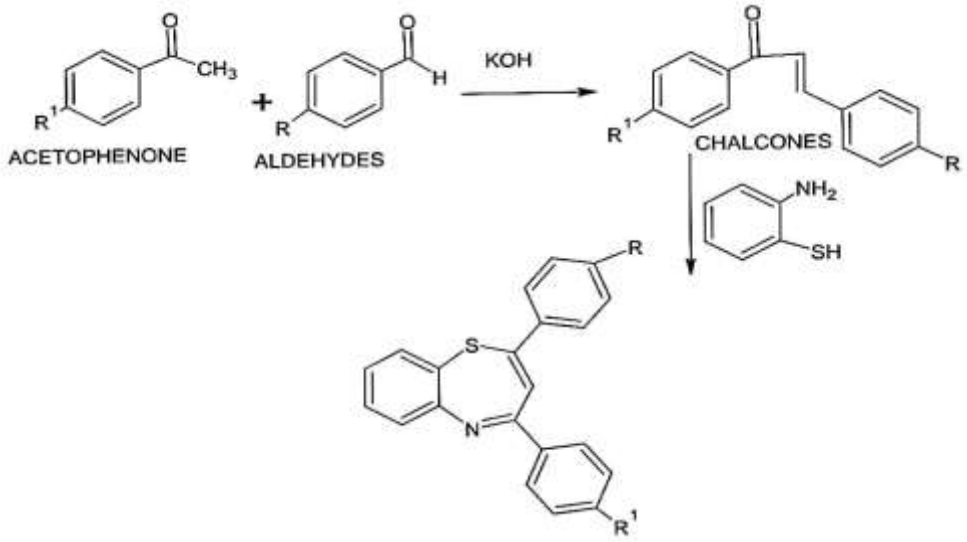
Scheme(5)

6. Myshkina,O.A.,*et al*[14]. focused on synthesizing a series of 4-substituted 2-trichloromethyl-3H-1,5-benzodiazepines and evaluated their antimicrobial and antinociceptive properties. The compounds were synthesized through the reaction of specific β-diketones with o-phenylenediamine, optimized for yield. X-ray diffraction studies revealed structural details, including molecular packing and halogen bonding interactions. The synthesized benzodiazepines showed varying degrees of antimicrobial and antinociceptive activities, with some compounds demonstrated notable effectiveness in these areas. The study also assessed the acute toxicity of these compounds, confirming their low toxicity.



Scheme(6)

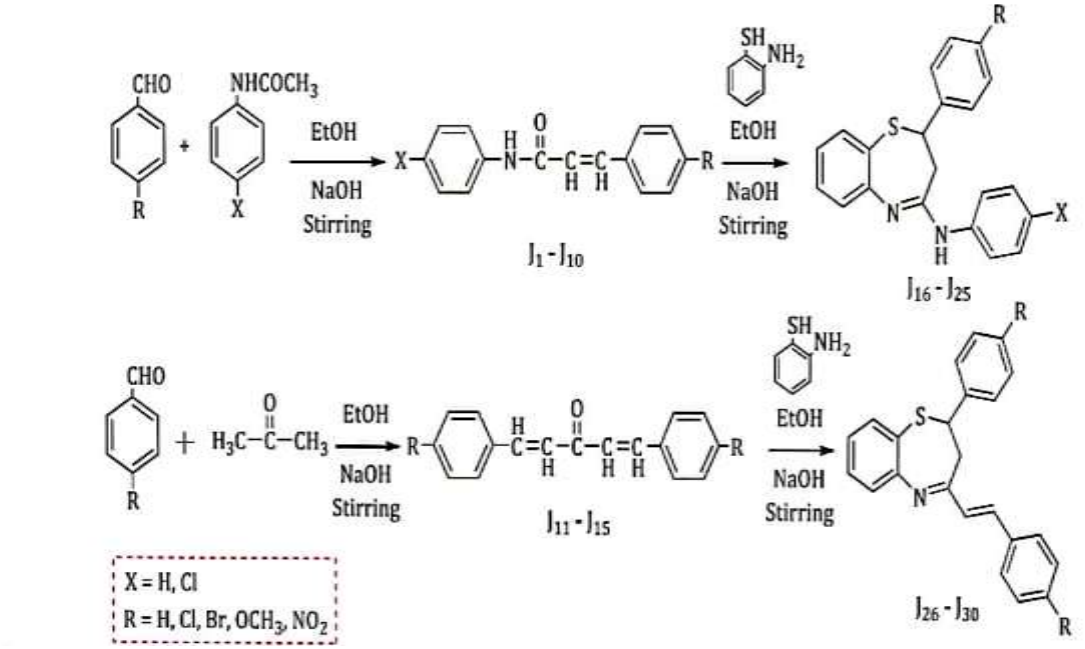
7. Merekar–Parjane, S. A., Merekar, A. N., & Dokhe, M. D[15]. have reported the design and synthesis of novel benzothiazepine derivatives and evaluates their potential as inhibitors of the Atu2422-GABA receptor. The compounds were prepared from substituted aromatic aldehydes and ketones, and characterized using various analytical techniques. Biological evaluations demonstrated promising inhibitory activity against the Atu2422-GABA receptor. Additionally, molecular docking studies were conducted to explore the binding interactions of these derivatives with the target protein.



1,5-benzothiazepines

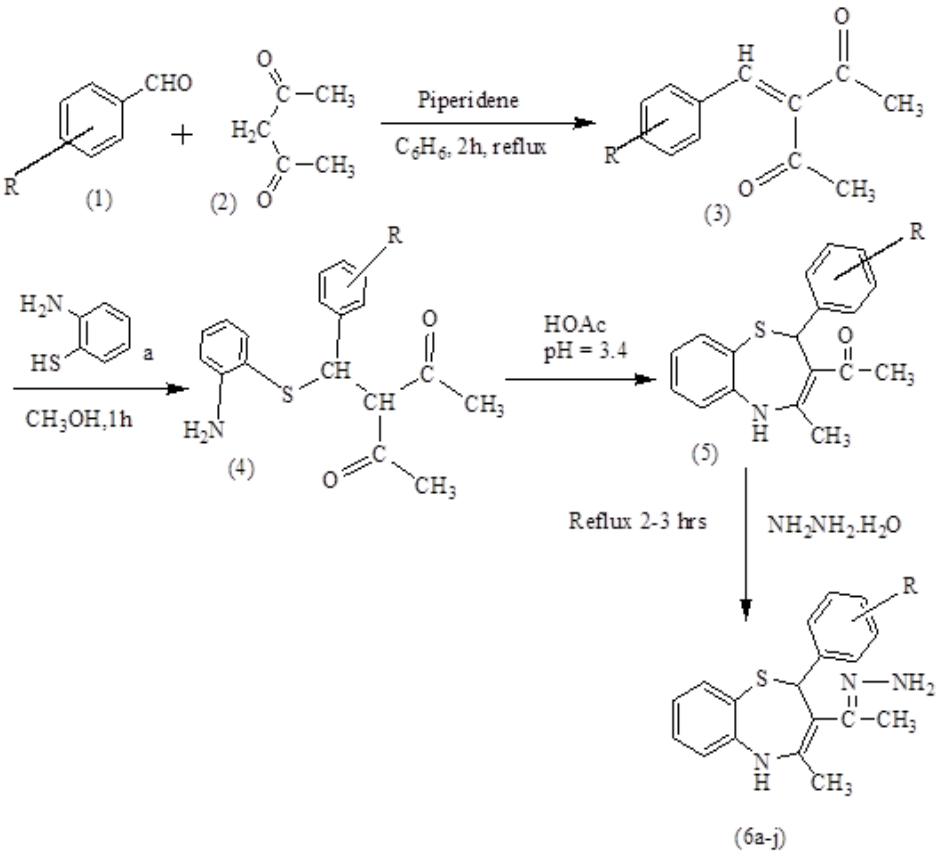
Scheme(7)

8. Jasim, Saad Salem, et al[16] . focused on synthesizing new 1,4-thiazepine compounds by reacting diphenyl acrylamides with diphenyl dienones in the presence of ortho-mercapto aniline. The reaction takes place in an alkaline medium using ethanol as a solvent. The synthesized compounds were identified through various spectroscopy techniques and their purity was confirmed by thin-layer chromatography. Their antibacterial activity was tested against several gram-positive and gram-negative bacteria, showing notable efficacy at higher concentrations.The study also explored the relationship between compound structure and antibacterial effectiveness, particularly highlighting the role of electron-withdrawing groups.



Scheme(8)

9. Chaudhri, V. K., Pathak, D., & Hussain, Z[17]. focused on the synthesis of new substituted 1,5-benzothiazepine derivatives designed to retain anticonvulsant properties while minimizing toxicity. Various compounds were synthesized and characterized using chromatographic and analytical methods. Their anticonvulsant activity was evaluated using the maximal electroshock model, with the most effective derivative identified. Additionally, the safety of this compound was assessed through neurotoxicity and acute oral toxicity testing. The aim is to develop novel, less toxic anticonvulsant agents.



Scheme(9)

5. Proposed Research Methodology:

Studying the New synthetic methods or modification in existing methodologies by using new reagents with emphasis on normalizing reactions conditions, increasing yields, rapid reactions will be studied.

1. Any two synthetic scheme for Pyrazoline.
2. Any two synthetic scheme for Benzodiazepines.
3. Any two synthetic scheme for Benzothiazepines.

   From Chalcones

6. The characterization of the compounds will be carried out using spectroscopic techniques such as:

i. IR

ii. ^{1}H NMR

iii. ^{13}C NMR

iv. Mass spectrometry.

7. Expected Outcomes of Research Work Proposed:

1. Development of efficient synthesis routes for preparing new Pyrazoline,Benzodiazepines and Benzothiazepines derivatives.
2. Study of the biological and pharmacological effectiveness of proposed new chemical compounds.
3. Publication of results in scientific journals to contribute to the field of chemistry.

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